An Open-source IVIVE Workflow Integrating QSAR and PK Models

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Many chemicals in commerce lack safety information. Accurate estimates of *in vivo* toxicity for these chemicals are needed to inform decisions on safe handling and use, as well as accidental exposure responses. High throughput *in vitro* assays provide a rapid way to evaluate potential chemical toxicity, but dose metrics and bioavailability need to be incorporated to allow interpretation and application of these data for risk assessment. To address this need, we have developed an open-source *in vitro* to *in vivo* extrapolation (IVIVE) workflow incorporating pharmacokinetic (PK) models with differing complexities. This workflow allows prediction of external administered dose corresponding to a predefined plasma concentration derived from *in vitro* assay data, or estimation of plasma concentration following a given dose. We developed a set of quantitative structure–activity relationship (QSAR) models to provide PK model input parameters such as fraction unbound to plasma proteins, Henry's constant, and partition coefficients. Evaluation of the QSAR models' performance yields R^2 values of 0.742-0.861 compared to experimental measurements. For chemicals lacking experimental PK parameter data, the QSAR predictions may be generated as part of the IVIVE workflow. Two case studies using the workflows, one focusing on assays measuring estrogenic activity and the other focusing on developmental toxicity, demonstrate how they provide a fast and straightforward approach to IVIVE analysis. This project was funded with U.S. Federal funds from NIEHS/NIH/HHS under Contract HHSN273201500010C.